Risk factors for mortality and failure of conservative treatment after aortic type B dissection

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Background: Despite medical treatment, one third of patients with uncomplicated type B aortic dissections experience severe late complications. The aim of this study was to identify patients at high risk of mortality during follow-up.

Methods: A total of 183 patients with acute Stanford type B dissection were treated in one of the university hospitals (Aachen [Germany], Maastricht [The Netherlands], and Innsbruck [Austria]) between 1997 and 2010. Records indicated that 120 patients were treated conservatively. Of these patients, 16 were lost to follow-up. The maximum diameter, extent of the dissection, and patency of the side branches were determined from computed tomography angiography data. Survival and treatment failure were analyzed by univariate and multivariate Cox regression analysis. The univariate analysis investigated the influence of aortic diameter ($\geq$41 vs <41 mm) on survival, and the multivariate analysis investigated the influence of aortic diameter, age, sex, and surgery on survival.

Results: During the follow-up period, the initial treatment was converted to surgical treatment in 21 patients (20.2%). Sixteen of the 104 patients (15.4%) died after a mean of 845.5 $\pm$ 805.9 days. The mean maximum aortic transversal diameter at admission was 41.2 $\pm$ 8.7 mm. The multivariate analysis identified aortic diameter ($P = .004$; hazard ratio, 1.07) and age ($P = .038$; hazard ratio, 1.05) as risk factors that significantly reduce survival.

Conclusions: Our study revealed both early aortic dilatation and older age as risk factors for increased mortality after conservative treatment of type B dissection. (J Thorac Cardiovasc Surg 2014;148:2155-60)

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Supplemental material is available online.

Despite medical treatment, one third of patients with type B aortic dissection have life-threatening complications, including death, rupture, increasing aortic diameter, and visceral or lower-limb ischemia, over the course of 5 years.[1,2] Data from the International Registry of Aortic Dissection (IRAD) reveal high mortality, with 1 in 4 patients dying within 3 years after acute type B dissection. After discharge, an estimated 31% to 66% of deaths are caused by dissection-associated complications, such as rupture or perioperative mortality from aortic repairs.[3-8]

The current criteria for primary surgical or endovascular repair of type B dissections include primarily life-threatening scenarios, such as rupture, malperfusion syndrome, progression of the dissection, enlarging aneurysms, and an inability to control blood pressure or symptoms.[7,9-12] The theoretic aim for thoracic endovascular aortic repair (TEVAR) in acute type B dissection is to remodel the architecture of the aortic wall by covering the proximal entry tear of the dissection and reexpanding the true lumen, thereby excluding the false lumen. Prophylactic TEVAR in uncomplicated type B dissections should prevent complications, particularly aneurysm enlargement. The first randomized study of elective stent-graft placement in survivors of uncomplicated type B aortic dissection, the INvestigation of STEnt grafts in patients with type B Aortic Dissections (INSTEAD) trial, did not reveal a difference in the 2-year cumulative survival between optimal medical therapy and TEVAR.[2] In contrast to these results after 2 years, the long-term results displayed an improved survival after TEVAR.[13] However, conservative treatment is still recommended for uncomplicated type B aortic dissection.[11,14]

However, the current therapeutic strategy of waiting until the criteria for surgical or endovascular repair are met

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Abbreviations and Acronyms

CTA	= computed tomography angiography
HR	= hazard ratio
INSTEAD	= INvestigation of STEnt grafts in patients with type B Aortic Dissections
IQR	= interquartile range
IRAD	= International Registry of Aortic Dissection
TEVAR	= thoracic endovascular aortic repair

seems to endanger some patients. In particular, patients with evolving transversal aortic enlargement are confronted with perioperative mortality and morbidity from subsequent aortic repairs or jeopardized by a substantial risk of rupture.[3,5,7,15] The aim of this study was to analyze the course of uncomplicated, conservatively treated type B dissections to identify patients with increased mortality during follow-up.

METHODS

Patients and Treatment

Between January 1997 and February 2010, 183 patients with an acute Stanford type B dissection as confirmed by multidetector computed tomography angiography (CTA) were admitted to 1 of 3 university hospitals in 3 specific centers. Among these patients, 63 (34%) had evidence of complications, such as rupture, excessive aortic enlargement, or visceral, renal, or extremity ischemia, and were referred for surgical or endovascular repair. Patients with uncomplicated type B dissection (n = 120, 66%) were admitted to the critical care unit, where their blood pressure was monitored and adjusted by optimal medical therapy (systolic arterial pressure <120 mm Hg) including a tailored antihypertensive regimen. Patients were switched to oral administration as soon as possible and closely observed for evidence of extremity, visceral, or renal malperfusion. Pain was treated according to World Health Organization guidelines. After discharge, the patients continued to receive oral antihypertensive therapy. CTA was performed at the time of diagnosis and repeated before discharge or in the case of complications. During follow-up, control computed tomography scans were performed after 3, 6, and 12 months and thereafter annually. The CTA data were analyzed by 2 independent investigators with regard to the maximum axial diameter of the aorta, extension of the dissection, and patency or thrombosis of the true lumen and the side branches. Among the patients who received initial medical treatment, 16 were lost to follow-up. This retrospective data analysis was performed according to our local ethics committee, and the data of 104 patients, including comorbidity and morphologic data, were reviewed.

Statistical Analysis

Continuous variables are expressed as mean values ± standard deviation or median and interquartile range (IQR). This article constitutes 2 time-to-event end points. The first time-to-event end point is "death," reflecting a classic survival setting. In addition, the time-to-event end point "treatment failure" was investigated. Treatment failure was defined as death or surgery after conservative treatment. Both end points were analyzed descriptively using Kaplan–Meier estimates, illustrated by the corresponding curves in Figures 1 and 2, and inferentially by univariate and multivariate Cox regression analysis. First, univariate Cox regression analysis was performed to investigate the influence of diameter (≥41 vs <41 mm) on both end points. Multivariate analysis was then performed to investigate the influence of diameter, age, gender, and, in case of survival, surgery. For the latter, after establishing a high-risk category (aortic diameter ≥41 mm and age ≥66 years), multivariate Cox regression analysis was performed to investigate the influence of this factor, gender, and surgery on survival. In all multivariate Cox regressions on survival, surgery was modeled as a time-dependent risk factor because of its change over time for a subset of the study cohort. The significance level was set at $\alpha = 0.05$. All Cox regression analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). Kaplan–Meier estimates and graphs were created using R (R Version 2.11.1, 2010, The R Foundation for Statistical Computing).

RESULTS

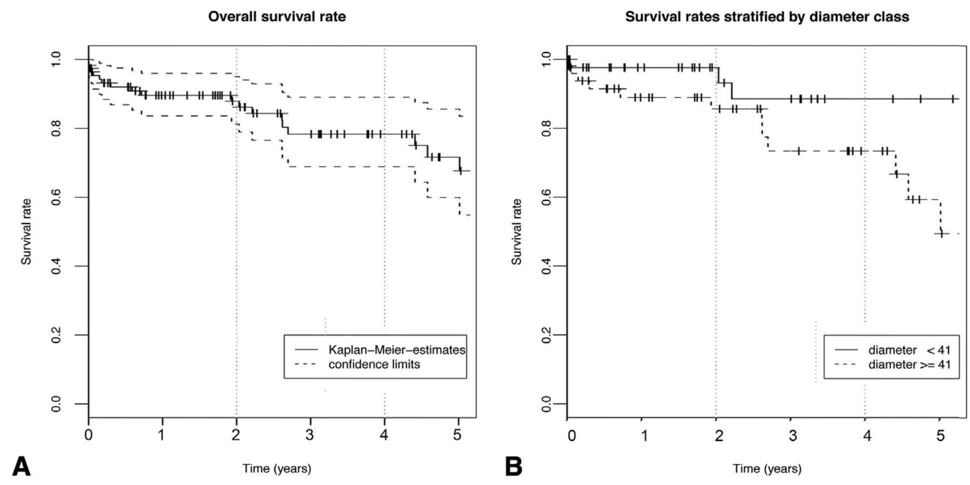
Patient Characteristics

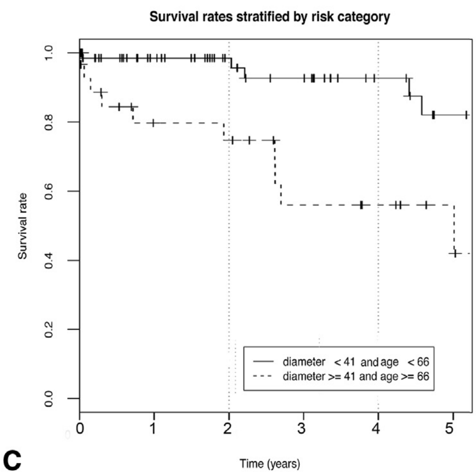
In the 120 patients with a mean age of 65.98 ± 11.2 years (range, 29-87 years) included in the database, the onset of symptoms was clearly assessable within the 14 days preceding admission and typical of aortic dissection. Diagnosis was established on the basis of computed tomography within 14 days of the onset of pain. At the time of the initial diagnosis, all patients were considered for medical treatment. Sixteen of these 120 patients were lost during follow-up. The study group included 74 men (70.8%) and 30 women (29.2%), and the comorbidities were diabetes in 7 of 104 patients, hypertension in 90 of 104 patients, coronary artery disease in 30 of 104 patients, renal insufficiency in 15 of 104 patients, smoking in 33 of 104 patients, and connective tissue disease in 3 of 104 patients. Three patients had an acute dissection superimposed on chronic aneurysms.

Conversion to Invasive Therapy

During the follow-up period, the initial medical treatment was converted to surgical treatment in 21 patients (20.2%) after a median of 333 days (IQR, 578 days; lower [25%] quartile value, 125 days; upper [75%] quartile value, 703 days; range, 1-1656 days) (mean, 488.7 ± 514.4 days). In 5 patients (4.8%), endovascular surgery was performed during the acute dissection phase (within 14 days) because of acute complications, despite the best medical treatment. Reasons for TEVAR were rapid extension of the transversal aortic diameter within 14 days (n = 2; 1 man aged 58 years, 1 woman aged 57 years), aortic rupture after 5 and 9 days (n = 2 men aged 78 and 63 years), and renal ischemia (n = 1 man aged 67 years). One of these 5 patients, a 63-year-old man, died of aortic rupture and subsequent hemodynamic shock 5 days after TEVAR.

In 16 patients (15.4%; 10 women), surgery was performed after a median of 189 days (IQR, 535.5 days; lower [25%] quartile value, 105.5 days; upper [75%] quartile value, 641 days; range, 1-1586 days) (mean, 631.8 ± 499.4 days). Surgical treatment was indicated because of aortic enlargement (n = 14), rupture (n = 1), or lower-limb ischemia (n = 1) (Table E1). Surgery





Multivariate Cox regression analysis		
Risk Factor	P-value	Hazard ratio
Aortic diameter	.0044	1.070
Gender	.1694	.421
Age	.0384	1.054
Surgery	.0253	4.188

D

FIGURE 1. Survival. A, Cumulative all-cause survival. B, Univariate analysis revealed a significant difference in the cumulative survival between patients with an aortic diameter ≥41 mm and patients with an aortic diameter <41 mm (P = .012). Kaplan–Meier estimates are presented in Table 1. C, Survival stratified by diameter and age. D, Multivariate Cox regression analysis.

included TEVAR (n = 2), endovascular aortic repair (n = 1), open repair of the infrarenal aorta (n = 2), Crawford type I repair (n = 2), type II repair (n = 6), type III repair (n = 1), and hybrid procedures (n = 2).

Diameter of Dissection

The mean maximum aortic transverse diameter on admission was 41.2 ± 8.7 mm. Two patient groups were created using the median of 41 mm as a cutoff, resulting in a group with a diameter less than 41 mm (n = 51) and a group with a diameter of 41 mm or more (n = 53).

Mortality

Sixteen patients (15.4%) died after a median of 774 days (IQR, 1252 days; lower [25%] quartile value, 38.5 days; upper [75%] quartile value, 1291 days; range, 2-2805 days) (mean, 826.6 ± 819.1 days). Two patients (both men) died of aortic rupture during the acute phase of dissection, despite the best medical treatment. One of these patients (aged 80 years) died 2 days after the dissection event. The other patient was aged 63 years; he sustained an aortic rupture 9 days after the initial dissection and was referred for emergency TEVAR. Five days after TEVAR, the patient died as a consequence of hemodynamic shock as noted earlier. Of the 14 patients who died during the chronic phase of dissection, 2 died of causes that were not dissection related. In 6 patients, the cause of death remains unknown. Therefore, a total of 6 patients died of dissection-related causes (rupture n = 4; intestinal ischemia n = 1; rupture after TEVAR = 1).

The cumulative all-cause survival at 1, 3, and 6 years was 89.6% (±3.2), 78.3% (±5.1), and 67.7% (±7.3), respectively (Figure 1, *A*). Univariate analysis revealed a significant difference in the cumulative survival between the 2 diameter groups (P = .012, Figure 1, *B* and Table 1) with a hazard ratio (HR) of 4.44 for a diameter of 41 mm or greater. The multivariate analysis identified aortic diameter (P = .004; HR, 1.07) and age (P = .038; HR, 1.05) as

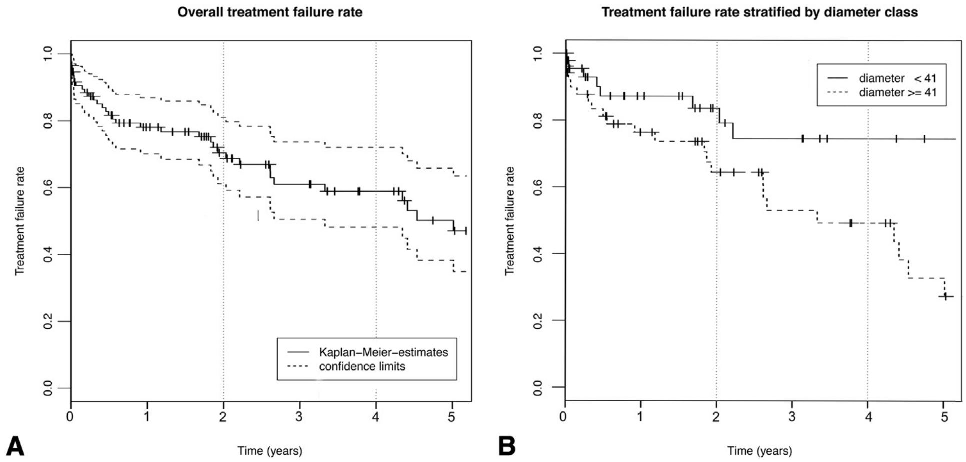


FIGURE 2. Treatment failure. A, Overall failure of conservative treatment. B, Failure of treatment stratified by diameter class revealed a significantly higher rate in patients with an aortic diameter ≥41 mm (P = .09; HR, 2.93). Kaplan–Meier estimates are presented in Table 2.

risk factors that significantly reduce survival (Figure 1, *D*). However, the age distribution between the 2 patient cohorts based on diameter was unequal, with older patients more likely to have a diameter of 41 mm or more. After correcting the binary risk factor, the HR for a diameter of 41 mm or more was 3.36 and not significant (P = .071). Another risk factor influencing survival was surgical treatment during the follow-up (Figure 1, *D*). Identification of diameter and age as risk factors motivated the formation of a high-risk patient cohort characterized by an aortic diameter of 41 mm or more and age 66 years or more. The cutoff level for age was set at the median of overall

TABLE 1. Mortality Kaplan–Meier estimates stratified by diameter group

Mortality stratified by diameter group					
Time (d)	No. at risk	Survival	Standard error	Lower 95% CI	Upper 95% CI
Diameter <41 mm					
14	42	0.976	0.0235	0.931	1.000
742	22	0.932	0.0488	0.841	1.000
807	20	0.885	0.0649	0.767	1.000
Diameter ≥41 mm					
2	53	0.981	0.0187	0.9452	1.000
23	45	0.959	0.0283	0.9055	1.000
54	44	0.938	0.0350	0.8713	1.000
109	41	0.915	0.0410	0.8378	0.999
261	36	0.889	0.0471	0.8017	0.986
705	27	0.856	0.0557	0.7539	0.973
954	21	0.816	0.0663	0.6954	0.956
956	20	0.775	0.0745	0.6417	0.935
984	19	0.734	0.0809	0.5913	0.911
1610	11	0.667	0.0973	0.5014	0.888
1672	9	0.593	0.1112	0.4108	0.856
1830	6	0.494	0.1293	0.2960	0.825
2805	2	0.247	0.1863	0.0564	1.000

CI, Confidence interval.

age values (65.98 years). In regard to death, multivariate Cox regression analysis revealed a significant (P = .0004) HR of 6.87. Figure 1, *C* illustrates the difference in regard to cumulative survival between the high-risk patient cohort (group aortic diameter ≥41 mm and age ≥66 years) and the remaining patients (age <66 years or aortic diameter <41 mm) (Figure 1, *C*).

Treatment Failure

After analysis of death and conversion to invasive treatment separately, we combined these 2 end points and addressed treatment failure of conservative treatment. A total of 32 patients had treatment failure due to death or conversion to invasive therapy after a median of 382 days (IQR, 883.5 days; lower [25%] quartile value, 70 days; upper [75%] quartile value, 953.5 days; range, 0-2805 days) (mean, 615.4 ± 686.9 days). Similar to the analysis of mortality, univariate analysis of the aortic diameter displayed a significant higher rate of treatment failure for patients with a larger aortic diameter (P = .11; HR, 1.038). In the diameter groups, an aortic diameter of 41 mm or more led to a significantly higher rate of treatment failure (P = .009; HR, 2.93) (Figure 2 and Table 2). Univariate analysis of gender and older age revealed no significant influence (gender: P = .116; HR, 0.56; older age: P = .92; HR, 1.00). The multivariate analysis, including diameter, gender, and older age, identified female gender (P = .047; HR, 2.131) and diameter (P = .004; HR, 1.05), but not older age (P = .662; HR, 0.992), as risk factors of treatment failure. However, the high-risk group (group aortic diameter ≥41 mm and age ≥66 years) showed no significant difference regarding treatment failure.

DISCUSSION

This study followed 104 patients with initial uncomplicated type B dissections and identified a patient group with

TABLE 2. Treatment failure Kaplan–Meier estimates stratified by diameter group

Time (d)	No. at risk	Survival	Standard error	Lower 95% CI	Upper 95% CI
Diameter <41 mm					
5	46	0.978	0.0215	0.937	1.000
14	41	0.954	0.0316	0.895	1.00
86	37	0.929	0.0399	0.854	1.000
150	33	0.900	0.0476	0.812	0.999
167	32	0.872	0.0538	0.773	0.984
613	24	0.836	0.0626	0.722	0.968
742	19	0.792	0.0732	0.661	0.949
807	17	0.745	0.0824	0.600	0.926
Diameter ≥41 mm					
1	52	0.981	0.0190	0.9441	1.000
2	51	0.962	0.0267	0.9107	1.000
5	48	0.942	0.0328	0.8794	1.000
13	44	0.920	0.0384	0.8479	0.999
23	43	0.899	0.0431	0.8182	0.987
54	42	0.877	0.0470	0.7898	0.975
109	40	0.855	0.0507	0.7615	0.961
125	39	0.833	0.0540	0.7341	0.946
180	38	0.812	0.0568	0.7075	0.931
199	35	0.788	0.0597	0.6795	0.915
333	32	0.764	0.0627	0.6501	0.897
431	28	0.736	0.0662	0.6175	0.878
669	24	0.706	0.0702	0.5808	0.858
681	23	0.675	0.0735	0.5453	0.836
703	22	0.644	0.0763	0.5109	0.813
953	17	0.606	0.0807	0.4673	0.787
954	16	0.569	0.0841	0.4255	0.760
972	15	0.531	0.0866	0.3854	0.731
1215	14	0.493	0.0883	0.3468	0.700
1586	9	0.438	0.0940	0.2877	0.667
1610	8	0.383	0.0969	0.2335	0.629
1656	7	0.329	0.0973	0.1839	0.587
1830	6	0.274	0.0952	0.1384	0.541
2805	2	0.137	0.1079	0.0292	0.641

CI, Confidence interval.

significantly increased mortality. Patients aged more than 66 years with a maximum aortic diameter greater than 40 mm at admission had a 6.87-fold higher mortality risk than younger patients and patients with smaller aortic diameters. Our findings are in agreement with Onitsuka and colleagues,[16] who examined the long-term outcome and prognostic predictors related to the development of complications associated with acute type B aortic dissection in 66 medically treated patients. A substantial difference was found in the initial maximum aortic diameter in patients with dissection-associated complications and patients with no complications.

Older patients generally take on a higher surgical risk than younger patients. Thus, if surgical procedures are required because of complications during the chronic course of a dissection, age seems to be a significant predictive risk factor. In their risk prediction model based on IRAD data, Suzuki and colleagues[17] identified hypotension/shock, absence of chest/back pain, and branch vessel involvement, but not age (≥70 years), as independent predictors of in-hospital death. Furthermore, age 70 years or more was not an independent predictor of death during long-term follow-up in another published analysis of IRAD data.[6] In contrast to the IRAD studies, the present analysis included age as a continuous variable, allowing more information and identifying it as an independent predictor of death. Data in the present study suggest that older patients take advantage of more aggressive therapy in the initial treatment of uncomplicated dissections to prevent conditions that necessitated later chronic phase surgery.

Multivariate analysis showed that later conversion to an invasive treatment significantly influenced survival. However, the study design does not allow a valid comparison between the groups in regard to invasive treatment. The need for surgical or endovascular treatment of an initially uncomplicated type B dissection is always an indicator of dissection-associated complications. Thus, extremely ill patients underwent operations. Moreover, invasive therapy carries an inherent risk of mortality, particularly in older patients; therefore, these patients have a greater risk compared with patients who do not require surgery during the course of dissection. Thus, influencing the course of dissection therapeutically is important to avoid the development of conditions that necessitate late surgical treatment. Aortic expansion was the most common complication leading to surgery in this study.

Because of morphologic conditions, endovascular or hybrid treatment was possible in only 6 of the 17 patients. Despite measures including cerebrospinal fluid drainage, distal and selective organ perfusion, and monitoring of motor evoked potentials, open surgery of extensive type B dissections causes serious surgical trauma and is associated with a high mortality.[18-20]

Furthermore, we combined mortality and conversion with invasive therapy and addressed treatment failure of conservative treatment of type B dissection. Although aortic diameter remained a risk factor, older age was not a significant risk factor in this analysis. However, the multivariate analysis revealed female gender as another risk factor for treatment failure of conservative treatment.

However, the absolute benefit of TEVAR over alternative treatments for chronic type B dissections remains unclear.[21] In the case of acute dissection, several studies have shown the potential of TEVAR in remodeling acute dissected descending aortic walls.[22-24] Furthermore, the INSTEAD trial confirmed that aortic remodeling due to TEVAR

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effectively results in significant aneurysm shrinkage after 2 years compared with medicamentously treated patients, but this effect had no significant influence on the survival in the TEVAR group. The 2-year cumulative all-cause survival of conservatively treated patients in the INSTEAD trial was 88.9% and comparable to our estimate of 87.9% in the present report.[2] In contrast to these results after 2 years, the results after 5 years revealed a reduction of mortality by TEVAR,[25] which may indicate a promising role of TEVAR in uncomplicated type B dissection.

CONCLUSIONS

In regard to mortality, the main finding of our study was the identification of a subgroup of patients at high risk (aortic diameter $\geq$41 mm and age $\geq$66 years), who had a 2-year survival of only 68.5%. In contrast, patients who did not fulfill the high-risk criteria displayed a cumulative survival of 95.7% after 2 years. Nevertheless, because of the retrospective, nonrandomized design of this report, conclusions from this multicenter analysis have to be drawn cautiously. Uncomplicated type B dissections in patients aged 66 years or more with a maximum aortic diameter greater than 41 mm on admission seem to present a higher risk of mortality. However, further studies are needed to determine with more certainty whether patients with uncomplicated type B dissections benefit from prophylactic TEVAR, particularly in older patients and in cases of early aortic dilatation.

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TABLE E1. Timing of intervention

Cases	Timing of intervention (d)	Kind of intervention
1	125	Type II repair
2	150	TEVAR with carotid subclavian bypass
3	167	Femoro-femoral bypass
4	180	EVAR with crossover bypass
5	199	Type I repair
6	207	TEVAR
7	261	TEVAR
8	431	Type I repair
9	613	TEVAR with carotid subclavian bypass
10	669	Type II repair
11	703	Type II repair
12	956	Type III repair
13	984	Type II repair
14	1215	AAA repair
15	1586	AAA repair
16	1656	Type II repair

AAA, Abdominal aortic aneurysm; *EVAR*, endovascular aneurysm repair; *TEVAR*, thoracic endovascular aneurysm repair.